REMARKS

Claims 1-4 and 6-13 are currently pending in the application. Claims 1, 8, 10, and 12 are in independent form. Applicant herein cancels claims 3-7 without prejudice. Support for the amendments to the independent claims can be found in paragraph [0035] ("By "PDE inhibitor" it is meant a compound that inhibits PDE. An example of such a compound is sildenafil (Viagra.TM.). A PDE inhibitor is an agent that reduces (e.g. selectively reduces) or eliminates the activity of a phosphodiesterase, such as PDE1-10 (e.g. type V phosphodiesterase, type 10 phosphosdiesterase), and any other phosphodiesterases."), and Example 1, paragraph [0091] ("Moreover, systemic administration of a phosphodiesterase type 5 inhibitor (Sildenafil) to rats 24 hours after stroke significantly increased angiogenesis in the ischemic boundary regions."). Further support can also be found in the rest of the Examples.

Applicants wish to express their appreciation for the courtesies extended Applicants' representative, Laura Dellal, during a personal interview conducted on September 23, 2008, with the Examiner and Supervisory Examiner.

Claims 1-13 stand rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. Specifically, the Office Action holds that isolation and culture of mesenchymal stem cells is disclosed as well as how phosphodiesterase inhibitors can be used to promote neurogenesis in rats, but not a patient in need of neurogenesis. The Office Action holds that there is no mention of how mesenchymal stem cells can be used to promote neurogenesis to a patient in need of neurogenesis promotion, and there are also no working examples of stem cells combined with a phosphodiesterase inhibitor promoting neurogenesis of increasing neurological function.

In response thereto, as previously stated in the Response of January 4, 2008, Applicant and others have demonstrated that ischemic stroke induces neurogenesis in the adult rat and mouse (see previous Response for references). Stroke-induced neurogenesis has also recently been demonstrated in the adult human brain, even in advanced age patients. Transplantation of rodent or human mesenchymal stromal cells (MSCs) substantially enhances neurogenesis and improves neurological functions after stroke in the rat. Based on these data, Applicant predicted that administration of MSCs promotes endogenous neurogenesis in stroke patients. Although there are no data showing that MSCs enhance neurogenesis in human patients, clinical trials in humans with stroke and spinal cord injury show that intravenous administration of bone marrow cells or direct transplantation of autologous whole bone marrow into the site of spinal cord injury improves neurological function significantly improves neurological function after stroke and spinal cord injury, respectively.

Rat models of disease are widely employed for the development of many treatments. The particular rat model of Applicant is an *in vivo* model. It is thus accepted methodology for one skilled in the art of neurogenesis to use the rat model of Applicant and apply results of the rat model to humans, because the results in the rat model are predictive of results in humans. Modern medical science emerges from the laboratory and from animal models of disease. While the examples of the present invention involve using the rat model, there are many instances throughout the specification when human application is described (see for example paragraphs [0044], [0054], [0057], [0083]). As a reminder, the USPTO does not have the same requirements of the FDA - there is no requirement in the USPTO that Applicant provide human data to establish enablement of the methods of the present invention. It is more than sufficient that the rat model is predictive of human results, and

Applicant submits a Declaration confirming this fact. Reconsideration of the rejection is respectfully requested.

Claims 1-4 and 6-13 stand rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. Specifically, the Office Action holds that there is no support for the phrase "identifying increased numbers of new neurons." In response thereto, Applicant points out paragraph [0049], explicitly providing support for the step of "identifying increased numbers of new neurons", emphasis added: "**Increased numbers of new neurons were identified** when this compound was administered at and beyond 24 hours after onset of stroke."

See also paragraph [0192], emphasis added: "BrdU (50 mg/kg-ip) was injected daily for 14 days after treatment in all groups. **BrdU is a thymidine analog that labels newly formed DNA and thereby identifies newly formed cells**. FIG. 9 shows that in the ipsilateral hemisphere subventricular zone, BrdU positive cells were significantly increased in the hMSC (2b, 40.6.+-.10.7) or/and NONOate (FIG. 9c, 43.6.+-.10.0/section; FIG. 9d, 67.4.+-.22.8/section) treated group compared to the control PBS treatment group (FIG. 9a, 29.8.+-.8.8/section) ($p<0.05$). BrdU found in the cytoplasm of macrophage-like cells were not counted. Double staining shows that the BrdU positive cells express the neuronal markers NeuN, neuron specific enolase (NSE) and the astrocyte marker GFAP. The percentage of BrdU reactive cells that express NeuN and GFAP proteins was approximately, 3%, 3% and 6%, respectively. These data indicate that that while individual subtherapeutic NO donor and MSC therapy failed to significantly increase neurogenesis compared to PSC control treated animals, combination therapy significantly promotes neurogenesis in ischemic brain."

Applicant has measured neurogenesis, i.e. identified increased numbers of new neurons, by using classic bromodeoxyuridine (BrdU) techniques along with double immunohistochemical labeling of BrdU with neuronal cell markers. One skilled in the art can perform such techniques to identify increased numbers of new neurons. Reconsideration of the rejection is respectfully requested.

Claims 1, 3, 5-8, 10, and 12 stand rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 6,075,028 to Graham. Specifically, the Office Action holds that Graham discloses a method of using a phosphodiesterase, sildenafil, to treat Tourette's syndrome and other related central nervous system (CNS) disorders. Promotion of neurogenesis and increasing neurological function would inevitably be involved by this treatment, since someone having Tourette's would be in need of neurogenesis promotion. Reconsideration of the rejection under 35 U.S.C. § 102(b), as anticipated by Graham, as applied to the claims is respectfully requested. Anticipation has always been held to require absolute identity in structure between the claimed structure and a structure disclosed in a single reference.

Graham does not disclose administering sildenafil to ischemic patients, but rather to Tourette's syndrome patients. The presently pending claims have been amended to require that the phosphodiesterase type 5 inhibitor is administered to ischemic patients.

The effects of sildenafil in Tourette's syndrome versus ischemia are quite different. Tourette's syndrome is a neuropsychiatric disorder. Stroke, neural injury, and certain neurodegenerative diseases are characterized by infarction – the death of brain tissue, i.e. neural damage. Tourette`s syndrome is not a form of neural damage or injury where cerebral tissue is infarcted. In Tourette`s, there are no neurological deficits and no evidence of any cell death or damage, only abnormal

behavior, in sharp contrast to ischemia. The etiology and pathophysiology of Tourette's is completely different from that of ischemia. Demonstrating that sildenafil can relieve or reduce tics associated with Tourette's is completely irrelevant to reducing neurological deficits caused by infarction after ischemia. Treatment of ischemia with sildenafil evokes neurogenesis and brain remodeling, mechanisms of action which cannot be inferred by the transient amelioration of behavioral symptoms present in Tourette`s patients. In other words, one cannot in any logical way extrapolate that reduction of tics in a neuropsychiatric disease would disclose or predict neurogenesis and recovery from a cerebral infarction.

Also, Graham discloses that sildenafil transiently reduces neurological symptoms of Tourette's syndrome because the symptoms return when administration of sildenafil is ceased. Graham does not provide any mechanisms underlying the effect of sildenafil on reduction of the symptoms. Nowhere in Graham is there any statement or inference to neurogenesis in the brain and brain plasticity with relation to ischemia. Applicant's data demonstrate that sildenafil enhanced-neurogenesis and functional outcome persist in ischemic rats for at least 20 days after termination of the use of the drug. In addition, Applicant demonstrates that agents which increase cGMP levels such as sildenafil act directly on neural progenitor cells in brain to induce the production of new neural cells.

The Office Action holds that "a way of identifying increased numbers of new neurons would be to recognize improvement in the disease after administration" with respect to Tourette's syndrome. Applicant respectfully disagrees, and provides a Declaration confirming the same. Neurogenesis is not a "necessary" condition for improvement of function. Improvement of function is achieved in Tourette's by other methods. Thus, improvement of function, i.e. reduction of tics, after treatment of Tourette's syndrome does not in any way imply causation by neurogenesis or the

presence of neurogenesis. Again, as stated above, there is no relationship between Tourettes syndrome, a disease without cerebral infarction, and ischemia (stroke), in which neurological deficits are caused by the death of cerebral tissue.

Applicant notes that no cited prior art reference to date has shown regeneration of neurons or new neuron growth. This was commonly accepted knowledge in the art at the time of the present invention, which is why the results of the present invention are so unexpected. Therefore, Graham cannot perform the required steps of claims 1, 8, 10, and 12 of "identifying increased numbers of new neurons", i.e. evidence of neurogenesis.

Therefore, since the Graham patent does not disclose or suggest promoting neurogenesis with a phosphodiesterase type 5 inhibitor in an ischemic patient or identifying increased numbers of new neurons as set forth in the presently pending independent claims, the claims are patentable over the Graham patent and reconsideration of the rejection is respectfully requested.

Claims 3 and 4 stand rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,827,740 to Pittenger. Specifically, the Office Action holds that Pittenger claims a composition of stem cells and a phosphodiesterase inhibitor. In response thereto, Applicant has canceled claims 3 and 4, rendering this rejection moot.

Claims 1-13 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Graham in view of International Patent Application Publication No. WO/2000/050568 to Price. Specifically, the Office Action holds that Graham teaches treating Tourette's syndrome by administering sildenafil. Since someone having Tourette's syndrome would be in need of neurogenesis promotion, the Office Action holds that it meets this

limitation. The Office Action holds that neurotransmission dysfunction is implicated with Tourette's, and Alzheimer's is also associated with neurotransmission dysfunction. The Office Action also holds that Price discloses a method of promoting neurogenesis or increasing neurological function (since they treat Alzheimer's) that includes cellular therapy. Therefore, the Office Action holds that it would have been obvious for one skilled in the art to use the cellular therapy of Price with the sildenafil of Graham. Reconsideration of the rejection under 35 U.S.C. §103(a), as being unpatentable over Graham in view of Price is respectfully requested.

"Any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed"; however, that reason must be present for the combination to be obvious. *KSR Intern Co. v. Teleflex*, 127 S. Ct. 1727, 1742, U.S. (2007). This requirement was confirmed in *Takeda Chem. Indust., et al. v. Alphapharm*, No. 06-1329 (Fed. Cir. 2007).

As stated above, Graham does not disclose all of the required elements of the presently amended independent claims, namely that a phosphodiesterase type 5 inhibitor is administered to an ischemic patient. Price also does not disclose treating ischemic patients but rather Alzheimer's. Therefore, combining Graham with Price would still not arrive at the present invention.

Furthermore, there is no reason why one skilled in the art would combine Graham and Price. Graham is concerned with Tourette's syndrome and symptoms, regardless of whether other diseases are mentioned. As stated above, in Tourette's, there are no neurological deficits, no neural damage, only abnormal behavior, in sharp contrast to stroke dealt with in the present invention. Treatment of stroke with sildenafil evokes neurogenesis and brain remodeling, mechanisms of action which

cannot be inferred by the transient amelioration of behavioral symptoms present in Tourette's patients. Thus, if anything, Graham is comparing the symptoms of Tourette's to some similar symptoms of Alzheimer's. A Tourette's patient is not in need of neurogenesis and does not have neural damage, thus one would not use the stem cells of Price to treat damaged brain because such damage is non-existent. In contradistinction, the presently pending claims relate to promoting neurogenesis and provide new neural growth in patients with neural damage, along with tissue growth from cellular therapy as well as requiring the step of identifying increased growth of new neurons. Therefore, it would not be obvious to combine Graham and Price to arrive at the present invention as claimed in the presently pending independent claims.

Since neither the cited references alone or in combination with knowledge in the art suggest the currently claimed invention, it is consequently respectfully submitted that the claims are clearly patentable over the combination, even if the combination were to be applied in opposition to applicable law, and reconsideration of the rejection is respectfully requested.

The remaining dependent claims not specifically discussed herein are ultimately dependent upon the independent claims. References as applied against these dependent claims do not make up for the deficiencies of those references as discussed above, and the prior art references do not disclose the characterizing features of the independent claims discussed above. Hence, it is respectfully submitted that all of the pending claims are patentable over the prior art.

In view of the present amendment and foregoing remarks, reconsideration of the rejections and advancement of the case to issue are respectfully requested.

The Commissioner is authorized to charge any fee or credit any overpayment in connection with this communication to our Deposit Account No. 11-1449.

Respectfully submitted,

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CERTIFICATE OF ELECTRONIC FILING VIA EFS-WEB

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I hereby certify that this correspondence is being electronically filed with the United States Patent & Trademark Office on the above date.

Terry Horst
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